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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/751,797	12/29/2000	Laure Dumoutier	LUD-5543.3 CONT.	5783

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/751,797	DUMOUTIER ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,7,8,10,14-16,18,19 and 50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 4, 7, 8, 10, 14-16, 18, 19, 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 12/11/03, has been entered.

Claims 1, 3, 4, 7, 8, 10, 14-16, 18-19 and 50 are pending.

Claims 2, 5, 6, 9, 11-13, 17 and 20-49 have been canceled previously.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's arguments, filed 12/11/03.
The rejections of record can be found in the previous Office Actions.

3. Upon a review of applicant's comments, it appears that the instant claims have the benefit under 35 U.S.C. § 120 to the instant application priority application USSN 09/354,243, filed 7/16/99.

Again, it does not appear to the previous priority USSN 09/178,973 supports the instant claims, particularly as it relates to "SEQ ID NOS: 24/25".

If applicant disagrees, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the parent application. Applicant is reminded that priority relies upon written support and enablement under 35 USC 112, first paragraph, for the instant claims.

4. It appears that applicant has acknowledged that the instant IL-TIF/IL-21 has been renamed IL-22 has been renamed by the relevant administrative authorities.

5. Claims 1, 3, 4, 7, 8, 10, 14-16, 18-19 and 50 stand rejected under 35 U.S.C. 112, first paragraph, because the specification,
while enabling for isolated nucleic acids which encode a T cell inducible factor which is a protein and which activates STAT3, which consists of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25 (and vectors, recombinant cells comprising said nucleic acids)
does not reasonably providing enablement for the broader recitation of
nucleic acids which encode a T cell inducible factor which is a protein and which activates STATS, the complementary sequence of which hybridizes under the claimed stringent conditions to at least one of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25 (and vectors, recombinant cells comprising said nucleic acids).

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 12/11/03, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant asserts the specification via its description of properties, sequence and hybridization conditions does disclose more than the specific sequences set forth in the in the sequence listings.

Applicant asserts that they do not have to supply a structural basis for the activation of STAT 3. Applicant relies upon a molecular weight range and a shared function of activation of STAT 3.

The following of record is reiterated for applicant's convenience.

The instant claims are drawn broadly to any nucleic acid that hybridizes to SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25 which encodes a T cell inducible factor (TIF) which is a protein and activates STAT3. However, the instant specification does not enable any such hybridizing nucleic acid broadly encompassed by the claimed invention.

It is noted that the claimed T cell inducible factor include T cell inducible factors (TIF) from other animal species, including other mammals as part of the invention (see page 29, lines 4-5 of the instant specification).

While applicant relies upon a molecule weight range, again it is noted that the claimed T cell inducible factors range from about 17-22 kD as determined by SDS-PAGE, which activate STAT proteins and in glycosylated form, these proteins range from 17 to about 30 kD, as determined by SDS-PAGE (see page 30, paragraph 2 of the instant specification).

Proteins encoded by the disclosed nucleic acids encompass immediate products of nucleic acid expression, glycosylated forms and multimeric forms comprising at least one protein of the invention or at least one different protein (see page 30, paragraph 1 of the instant specification).

Applicant has not disclosed an isolated nucleic acid molecule which encodes a T cell inducible factor (TIF) which activates STAT3, as recited in the instant claims, other than T cell inducible factors encoded by nucleic acid molecules consisting of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25.

Neither has applicant disclosed the structural basis or nexus for activation of STAT 3 by the T cell derived inducible factor (TIF) encoded by the disclosed nucleic acids consisting of cDNA and genomic sequences of TIF.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies any mammalian T cell inducible factor. T cell inducible factor may have some notion of the function of the protein, however, there is insufficient guidance and direction as how to make and use the claimed genus of T cell inducible factors, commensurate in scope with the claimed invention. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

While applicant relies upon a common function of inducing STAT 3, applicant has not addressed the diversity of structure and function of T cell inducible factors disclosed and not disclosed in the specification as filed with any specificity.

For example as pointed out previously, the specification discloses a diversity of structure and function of the disclosed T cell inducible factors encoded by nucleic acid molecules consisting of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25.

It is noted that the instant specification discloses that mouse TIF beta and mouse TIF alpha respond differently in response to IL-9 (e.g. see Examples 12-14 on pages 15-17 of the instant specification).

Although the instant specification discloses high homology between mouse TIF alpha and beta (and therefore hybridizes to mouse TIF alpha under stringent conditions), there is insufficient guidance and direction as to critical common structural elements that define a T cell inducible factor or that define a T cell inducible factor alpha or beta and, in turn, the nexus between structure in an T cell inducible factor and its ability to stimulate the expression of STAT 3.

T cell inducible factors, including those encoded by SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25., which stimulate STAT 3, that is, they are not related as a ligand-receptor binding pair.

Applicant does not appear to understand this issue. In addition to the other issues of record and reiterated herein, it is noted that applicant's reliance upon STAT 3 activation is based upon a downstream functional readout and not a direct link to T cell inducible factors(e.g. ligand-receptor binding pair) and not a nexus of a particular structure of T cell inducible factors that results in STAT 3 activation.

Consistent with the Examples in the instant specification (e.g. Examples 21 and 27), it is noted that the co-inventors have published the same or similar results disclosed in the specification as filed. For example, see Dumoutier et al. PNAS 97: 10144-10149, 2000 and Dumoutier et al., J. Immunol. 164: 1814-1819, 2000.

For example, the co-inventors have disclosed that the biological activities of T cell inducible factors remain illusive (Dumoutier et al. PNAS 97: 10144-10149, 2000; see entire document, particularly, page 10144, column 1, paragraph 1 of the Introduction). Further, this reference discloses that while IL-9 was useful in initially identifying mouse T cell inducible factor, T cell inducible factor does not appear to play a major role in the in vivo biological activities of IL-9 (see Discussion, page 10149, column 1, paragraph 1). Here, too, the reference distinguishes mouse from human T cell inducible factor as well as from in vitro and in vivo studies of T cell inducible factor (see Discussion). This discrepancy between in vitro and in vivo T cell inducible factor induction might reflect an indirect mechanism of gene induction and that further studies are needed to elucidate the mechanisms of regulating T cell inducible factor (see Discussion).

This distinction between IL-9 and T cell inducible factors differs from the instant disclosure which states that T cell inducible factor is a marker for the expression or effect of IL-9 in a subject (see page 6 of the instant specification).

The co-inventors have disclosed that the mouse T cell inducible factors (TIF) were found to induce to STAT 3 and 5 activation in mesangial and neuronal cell lines but failed to reproduce activities such as the induction of proliferation of T helper clones, mast cells or inhibition of corticoid-induce apoptosis (Dumoutier et al., J. Immunol. 164: 1814-1819, 2000; see entire document, including Abstract and Discussion) (also see Example 21 of the instant specification).

In contrast to mouse IL-TIF, human IL-TIF induced STAT 1 and 3 in human hepatoma cells (see (Dumoutier et al. PNAS 97: 10144-10149, 2000) (See Example 27 of the instant specification).

It is noted that the starting material of peripheral blood cells for human TIF was stimulated with anti-CD3 antibodies and not IL-9 (see page 23, paragraph 1 of the instant specification). Anti-CD3 antibodies can stimulate a variety of molecules and are not limited to stimulating TIF alpha or beta. The instant specification further discloses that TIF mRNA can be expressed in the absence of IL-9 (see Example 14, particularly page 17, lines 7-8 of the instant specification.

In addition, it is noted that the "T cell inducible factor" has been renamed "IL-TIF/IL-21", which, in turn, has been renamed "IL-22" by the coinventors (see page 1, column 1, Background and Prior Art of Renauld et al., US 2003/0012788 A1). Here, it is noted that the conventors have shown that the signaling pathways associated with IL-22 were not the same as IL-10, as previously thought (see entire document, including page 1, column 2, paragraph 2).

Furthermore, Ebert (Trends in Immunology 23: 341-342, 2002) notes confusion and ambiguities in labeling cytokines as interleukins, including IL-TIF/ IL-21 described by the instant inventor Dumoutier.

Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) disclose that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

Applicant is relying upon certain biological activities and the disclosure of this limited number of mouse and human T cell inducible factor species to support an entire genus of nucleic acids encoding T cell inducible factors that stimulate STAT3 activation. Yet the instant specification does not provide sufficient guidance and direction how to make and use any nucleic acid that encodes a T cell inducible factor that stimulates STAT3 activation, as encompassed by the claims. Also, the specification does not provide for the correlation or nexus between the chemical structure and the function of the genus of T cell inducible factors or nucleic acids encoding T cell inducible factors, currently encompassed by the claimed invention. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and activities.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. T cell inducible factor) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a limited number of T cell inducible factor sequences from mouse and human and in turn utilizing predicted structural determinations to ascertain functional aspects of the genus of nucleic acids encoding T cell inducible factors and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Because of the lack of sufficient guidance and predictability in determining which structures would lead the skilled artisan to make and use the genus of nucleic acids encoding T cell inducible factors (TIFs) which stimulate STAT3 in the claimed invention other than those disclosed in the specification as filed with the desired properties and that the relationship between the sequence of a T cell inducible factor encoding a functional T cell inducible factor amino acid or nucleic acid structure as the relationship between structure-function was not well understood and was not predictable. Also, see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of nucleic acids encoding T cell inducible factors which stimulate STAT3 activation in the claimed invention.

In the absence of sufficient guidance and direction to the structural and functional analysis, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue to make and use nucleic acids encoding T cell inducible factors which stimulate STAT 3 activation, under the high stringency conditions other than those disclosed as SEQ ID NOS 7, 8, 24 and 25 in the specification as filed

It is acknowledged that the instant specification does describe methods for screening and evaluating nucleic acid molecules that encode nucleic acid molecules which encode T cell inducible factors (TIFs) which also induce STAT3 activation.

However, the instant application does not provide the necessary link between these steps of screening and evaluating nucleic acids encoding T cell inducible factors. There is insufficient guidance in the way of selecting an T cell inducible factor without the need of undue experimentation. The instant application provides assays for determining whether a nucleic acid encodes a protein with certain desired characteristics (e.g. activates STAT3) and identifies certain specific T cell inducible factors from two mammalian species (mouse and human).

These descriptions without more precise guidelines amount to little more than a starting point, a direction for further research. The specification provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute enablement for the scope of the claimed T cell inducible factors encompassed by the claimed invention.

Neither the specification nor the prior art provides a structural basis for the recited activity of the encoded protein. Without such guidance, predicting the structure that defines a TIF-IL/TIF-21 other than those IL-TIF/IL-21 encoded by SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25, and which possesses the claimed biological activities of stimulating STAT activation or acute phase production (other than an IL-TIFs/ IL-21 encoded by nucleic acid molecule consisting of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25), is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986). In re Fisher, 166 USPQ 19, 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Therefore, there is insufficient evidence of record to show that one skilled in the art would be able to practice the scope of the claimed invention as claimed without an undue amount of experimentation.

Consequently, the experimentation left to those skilled in the art to determine which nucleic acid sequence variants of SEQ ID NOS: 7, 8, 24 and 25 would still maintain the properties of a T cell inducible factor (TIF) that activates STAT3 would have been unpredictable and, in turn, would have been unnecessarily, and improperly, extensive and undue. The instant application does not describe the claimed invention in terms that will enable the skilled artisan to make and use the invention, commensurate in scope with the claimed invention.

Applicant's arguments have not been found persuasive.

6. Upon an updated sequence search, it does not appear that SEQ ID NOS. 1-4 and 28-31 recited in the claims of Ebner et al. (US 2003/0003545 A1) read on the instant SEQ ID NOS. and upon the provision of the declaration by the coinventors filed 12/11/03; the previous rejection under 35 U.S.C. § 102(e) as being anticipated by Ebner et al. (US 2003/0003545 A1) as further evidenced by Renauld et al., US 2003/0012788 A1), which discloses that the instant T cell inducible factor has been named "IL-TIF/IL-21" and, in turn, has been renamed "IL-22" (see page 1, column 1, Background and Prior Art of Renauld et al., US 2003/0012788 A1), has been withdrawn.

Given applicant's admission that the instant claims encompass IL-22 encoding nucleic acids, applicant is invited to clarify the relationship or distinction between the IL-22 molecules disclosed by Ebner et al. (US 2003/0003545 A1) (e.g. see page 39, paragraph 0272), where Ebner et al. disclose "IL-22 (SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 30 and SEQ ID NO: 31) and yet the claimed sequences of the instant claims do not appear to be similar to SEQ ID NO 3, 4, 30 and 31 of Ebner et al.

7. No claim allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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